

XLA

X-linked agammaglobulinemia (XLA)

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About this booklet

This booklet provides information on X-linked agammaglobulinemia (XLA). It has been produced by the PID UK Medical Advisory Panel and Patient Representative Panel to help answer the questions patients and their families may have about this condition but should not replace advice from a clinical immunologist.

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Summary

X-linked agammaglobulinemia (XLA; also known as Bruton's agammaglobulinemia) is the name for a condition that affects the body's ability to make antibodies and fight infections. It belongs to a group of conditions known as antibody deficiencies. XLA affects only boys and its features include repeated episodes of bacterial infections affecting the ears, sinuses, nose, eyes, skin and the gastrointestinal tract. It is a rare condition with about 5-10 people in a million affected.

Antibodies belong to a particular type of protein, called immunoglobulin, normally found in blood and body fluids. There are three major types of immunoglobulin, known as:

- **Immunoglobulin G (IgG)** – the most abundant and common immunoglobulin, found in blood and tissue fluids. IgG functions mainly against bacteria and some viruses.
- **Immunoglobulin A (IgA)** – found in blood, tears and saliva. It protects the tissues of the respiratory, reproductive, urinary and digestive systems.
- **Immunoglobulin M (IgM)** – found in the blood. IgM functions in much the same way as IgG but is formed earlier in the immune response.

All types of immunoglobulin are made up of antibodies against the germs that an individual has met during the course of his or her life.

Antibodies are made by white blood cells called B-cells or sometimes referred to as B-lymphocytes. In XLA there are genetic changes, known as mutations, in the Bruton's tyrosine kinase (BTK) gene. These mutations block the development of normal, mature B-cells that would normally make antibodies. As a result, people with XLA have very few mature B-cells and cannot make immunoglobulins; that is, the antibodies that are needed to protect the body against infections.

The aim of treatment in XLA is to replace the missing or defective antibodies with purified immunoglobulins from the blood of healthy donors in order to reduce the frequency and severity of infections. Although not a cure for XLA, immunoglobulin replacement therapy is often enough to keep patients healthy so that those affected can lead full and relatively normal lives. Children with XLA should take part in regular school activities, including exercise, and do not need to be limited in what they can do. It is important for the school to be aware of the diagnosis, however.

Antibiotics are often needed to treat breakthrough bacterial infections that will occur from time to time. A few individuals may need to take antibiotics every day to protect them from infection or to treat chronic sinusitis or chronic bronchitis. Patients with bronchiectasis (widening and scarring of the bronchial airways) may need help from a physiotherapist to help clear their airways.

How did I/my child get XLA?

XLA is caused by mutations in the BTK gene that is present on X chromosomes. The BTK gene makes the enzyme Bruton's tyrosine kinase, which is needed to instruct B-cells to mature and produce antibodies.

More than 600 different mutations in the BTK gene have been found to cause XLA. Most mutations result in the absence of the BTK enzyme or in an abnormal BTK protein that is quickly broken down in the cell. Without functional BTK enzyme there is no development of B-cells – and so a lack of antibodies – and this results in an increased susceptibility to bacterial infections.

XLA is an inherited condition, meaning it is passed down through the generations. It follows what is called an X-linked recessive pattern of inheritance, with transfer of a defective gene on one of the two X chromosomes of a mother to a son. This means that for every boy who is conceived to a carrier mother there is a 50/50 chance that he will have XLA. This has implications for family planning. Mothers, their maternal aunts and sisters may be carriers and should receive genetic counselling. Daughters who are born to carrier mothers should also be tested once they are old enough to give informed consent as there is a 50/50 chance they might carry the faulty gene. Affected fathers will pass on the faulty gene to all of their daughters, who will be carriers of XLA, but their sons will not be affected by XLA or be carriers of the condition.

Family planning and XLA

Prenatal genetic diagnosis is available for families in which XLA has already been diagnosed. Your health team will be able to refer you for advice about the risks of prenatal testing.

What are the symptoms of XLA?

Boys with XLA develop bacterial infections because they lack protective antibodies. Infections usually affect those surfaces that are exposed to bacteria, such as the tissue surfaces that line the lung and gut.

In XLA serious bacterial infections may occur, such as meningitis or pneumonia. Such infections usually begin in infancy or early childhood, typically at 6 to 9 months of age when the protective antibodies that have been passed from the mother to the unborn child via the placenta are broken down. This leaves an affected boy with no antibodies for fighting infections.

People with XLA can have repeated, severe or persistent infections. Here are some common features that you may recognise and which may have led your clinician to a diagnosis of XLA:

- Sinusitis – inflammation of the air-filled spaces (paranasal sinuses) that surround the nose
- Inner ear infections, such as otitis media
- Throat infections, such as tonsillitis or laryngitis
- Chest infections, such as bronchitis or pneumonia
- Stomach and intestinal infections, including giardiasis (a parasitic infection) resulting in persistent diarrhoea or weight loss
- Skin infections, such as abscesses and boils
- Eye infections, such as conjunctivitis
- Urinary tract infection (cystitis)
- Meningitis
- Joint infections (osteomyelitis)
- Blood poisoning (septicaemia).

Furthermore, very small or absent tonsils and lymph nodes (the glands in the neck) may be a physical sign of XLA, since these are the sites where the B-cells would normally be present.

What are the common causes of infection in XLA?

Infections affecting the lungs, ears and sinuses are commonly caused by these organisms:

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus*

and infections in the gut by:

- *Campylobacter*
- *Salmonella*
- *Giardia*.

People with XLA are usually able to cope with most viral infections, including measles and chicken pox, without any problems. In rare cases enteroviruses, such as polio, can cause serious infection but this is uncommon for those on adequate replacement immunoglobulin therapy.

How is XLA diagnosed?

Antibody deficiency will be considered in individuals presenting with repeated, severe or persistent infections. These individuals will usually be referred to a specialist for further assessment, following which an immunologist should be consulted.

Making the diagnosis

A clinical immunologist usually makes the diagnosis of XLA.

Diagnosis is confirmed by blood tests. Tests may be intensive at the beginning of this investigative process and may include an assessment of:

- The levels of IgG, IgA and IgM
- The function of any antibodies that are present, to see how well they react to microbes, if at all (unlikely in XLA). This is done by test immunisations using safe 'dead' or fragmented organism vaccines
- How many lymphocytes (the white blood cells involved in immunity) there are in the blood
- How many B-lymphocytes are present in the blood, as well as the other major type of lymphocytes (needed to fight viruses) known as T-cells. In XLA, mature B-lymphocytes are not present in blood but T-cell levels will be normal.

A definite diagnosis is made by looking for mutations in the BTK gene using genetic analysis. When a specific defect is found, the doctors will often test female members of the family to diagnose those who carry the abnormal X chromosomes.

Treatment

At present there is no cure for XLA but affected boys can grow up to lead normal productive lives if they keep to the treatments recommended and have regular check-ups with an immunologist.

The main treatment for XLA involves replacing the missing antibodies using immunoglobulin (Ig) replacement therapy. This treatment can be given intravenously (dripped into a vein through a needle in the arm or hand) or subcutaneously (injected under the skin in the lower stomach or thigh). This treatment is usually needed every day or every week for subcutaneous therapy or every 2-4 weeks for intravenous therapy, depending on the individual. The dose is monitored by looking at how well the treatment protects against infections, since adequate therapy reduces the rate and severity of bacterial

infections and may prevent them entirely. The doctor will also do blood tests periodically (typically every 3-6 months, although this may be more frequent depending on your centre's local policies) to check levels of IgG and for any possible complications.

Additional treatments focus on taking steps to reduce the number and severity of infections. They include prompt long-term treatment with broad-spectrum antibiotics or more specific antibiotics if the bugs causing the infection are known. If lung problems have developed, such as bronchiectasis, where the airways of the lungs become abnormally widened leading to a build-up of excess mucus, physical therapy, such as physiotherapy and specific exercises, may be needed to remove the mucus from the lung airways.

Are there any associated health problems with XLA and how will my/my child's health be monitored?

Some people with XLA, but not all, may have or may develop other health problems. Monitoring is usually by clinical review (check-up), infrequent blood tests and, for some people, tests of breathing function.

Your clinical immunologist will be on the look out for the complications and will work with other clinical specialists to offer you the most appropriate advice and treatments.

Lung and sinus problems

If chronic lung or sinus disease, such as bronchiectasis, has developed before diagnosis, those affected may have a reduced ability to exercise. Your doctor may refer you for 'lung function tests'.

Lung function tests measure how well your lungs are working. You may be referred to a physiotherapist, and specific exercises may be recommended to remove the mucus from the lung airways to improve your lung health. People with chronic sinus disease may be referred to an ear, nose and throat (ENT) specialist for advice on other treatments, including physical treatments, to reduce the risk of further sinus damage.

Painful joints and arthritis in XLA

Joint disease (arthritis) usually affecting the knees can occur. This usually only occurs in individuals not receiving immunoglobulin replacement therapy and is thought to be related to infection with enteroviruses and mycoplasma.

Gut problems in XLA

Inflammatory bowel disease (such as Crohn's disease) can occur in XLA and is thought to be a complication of repeated, severe or persistent bowel infection.

Other problems

Sometimes a condition known as neutropenia – a reduction in the number of neutrophils (a type of white blood cell) – can happen. This is usually temporary and is seen only in individuals not receiving immunoglobulin replacement therapy.

Immunisation

Not all vaccines are safe to be administered to patients with XLA and therefore you should discuss any recommended or required vaccinations with your clinical immunology team before a vaccine is given.

More questions about XLA?

Then type 'FAQs on XLA' into the 'I'm looking for...' section of the home page of our website at www.piduk.org.

More information about the genetic aspects of XLA is available in our booklet 'Genetic aspects of primary immunodeficiency' available at www.piduk.org/static/media/up/geneticaspectsopid.pdf

Glossary of terms

abscess – a collection of pus that has built up within a tissue of the body.

antibody – a type of protein (immunoglobulin) that is produced by certain types of white blood cells (plasma cells – a type of B-cell). The role of antibodies is to fight bacteria, viruses, toxins and other substances foreign to the body.

B-cell – a type of white blood cell (lymphocyte) that produces antibodies.

bronchial – part of the airway system that carries air into the lungs.

bronchiectasis – a widening of the tubes (bronchi) that lead to the air sacs of the lung; this can happen because of repeated bouts of infections.

carrier – an individual who carries the abnormal gene for a specific condition, usually without showing symptoms.

chromosome – a long threadlike strand of DNA that carries a set of genes. Normally humans have 23 pairs of chromosomes.

chronic – a chronic condition is a health condition or disease that is persistent or otherwise long-lasting in its effects, or a disease that comes with time.

deficiency – a lack or shortage.

enterovirus – a type of virus that enters the body through the gut.

enzyme – a protein that carries out biological reactions in the body.

gastrointestinal tract – the lining of body parts that run from the mouth to the bottom. It can also be referred to as the gut.

gene – the fundamental unit of inheritance that carries the instructions for how the body grows and develops.

genetic analysis – a study of the genetic code (DNA) that makes genes.

genetic counselling – a service that provides information and advice about genetic conditions to people and their families to help with family planning.

immunoglobulins – proteins (globulins) in the body that act as antibodies. They work to fight off infections. They are produced by specialist white blood cells (plasma cells/B-cells) and are present in blood serum and other body fluids. There are several different types (IgA, IgE, IgG and IgM), and these have different functions.

inheritance – the passing down of genetic information from parents to children.

intravenous – inside or into a vein; e.g. an immunoglobulin infusion may be given directly into a vein.

lymph nodes – small bean-sized organs of the immune system distributed widely throughout the body. They are the home for the many types of cells that are important in fighting infections.

lymphocyte – a white blood cell that works to fight infection in the body. One type of lymphocyte is called a ‘B-cell’. This type of lymphocyte makes antibodies.

mutation – a permanent alteration to a gene where part of the DNA within the gene is different from what it should be. There may be an extra or missing part, for example. Mutations may affect the proper growth or development of a person. They can have either positive or negative effects on an individual.

mycoplasma – a type of bacteria.

organism – a single-celled life form; e.g. a bacteria, virus or fungus. It can also mean an individual plant or animal.

placenta – the organ attached to the lining of the womb during pregnancy. It provides the nutrition and oxygen to the growing baby.

plasma – the liquid component of blood without the cells (but with all the proteins).

plasma cell – a specific subtype of B-cell that is found within the bone marrow or lymph nodes. Plasma cells are responsible for the majority of high-quality antibody production.

prenatal genetic diagnosis – diagnostic tests that will find out if a developing baby has a genetic condition.

protein – one of the basic building blocks of life. Proteins make up the structure and determine the function of the cells that make up all the tissues of our bodies.

sinuses – air-filled spaces within the bones of the face and around the nose. Infection of the sinuses is called sinusitis.

subcutaneous – under the skin; e.g. an immunoglobulin infusion may be given under the skin in the lower stomach or thigh.

T-cell – a type of white blood cell (lymphocyte) that helps the immune system work properly to fight infection.

X chromosome – the chromosome that helps determine whether you are male or female. A female has two X chromosomes, whereas a male has one X chromosome and a Y chromosome.

X-linked recessive pattern of inheritance – a type of inheritance where a recessive gene on the X chromosome is passed down to children. Generally boys/men display full symptoms of the condition and girls/women do not have any symptoms. This is because females have two X chromosomes and only one of them has a faulty gene. The other, unaffected X chromosome can generally compensate for the faulty gene in the first X, masking any symptoms. Males display the full symptoms because they have one X and one Y chromosome – the Y chromosome can’t compensate for the recessive genes that are carried on the X chromosome.

Notes

About Primary Immunodeficiency UK

**Primary Immunodeficiency UK
(PID UK) is a national organisation
supporting individuals and families affected
by primary immunodeficiencies (PIDs).**

We are the UK national member of the International Patient Organisation for Primary Immunodeficiencies (IPOP), an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

Our website at www.piduk.org provides useful information on a range of conditions and topics, and explains the work we do to ensure the voice of PID patients is heard.

If we can be of any help, please contact us at hello@piduk.org or on **0800 987 8986** where you can leave a message.

Support us by becoming a member of PID UK. It's free and easy to do via our website at www.piduk.org/register or just get in touch with us. Members get monthly bulletins.

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